THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Basket Trials Revisited: Faster, Better, Smarter Trials. Precision Medicine: Insights, Challenges and Perspectives in Academia

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Disclosures

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Advisory Board/Consultant: Roche, Europe; Covance; Genentech

Initiative for Molecular Profiling in Advanced Cancer Therapy (IMPACT)

Hypothesis, 2007

- Selection of therapy based on patients' tumor molecular analysis will improve clinical outcomes compared to the standard approach

Methods

- Patients who exhausted standard treatment options or had incurable rare cancers were referred to our Phase I program for treatment.
- CLIA-certified tumor molecular testing in consecutive patients referred for treatment.
- Genes analyzed: 1-50, depending on time of testing
- Trials available against various targets
- Treatment: matched targeted therapy, if available; if unavailable, non-matched.
- Retrospective analysis, exploratory.

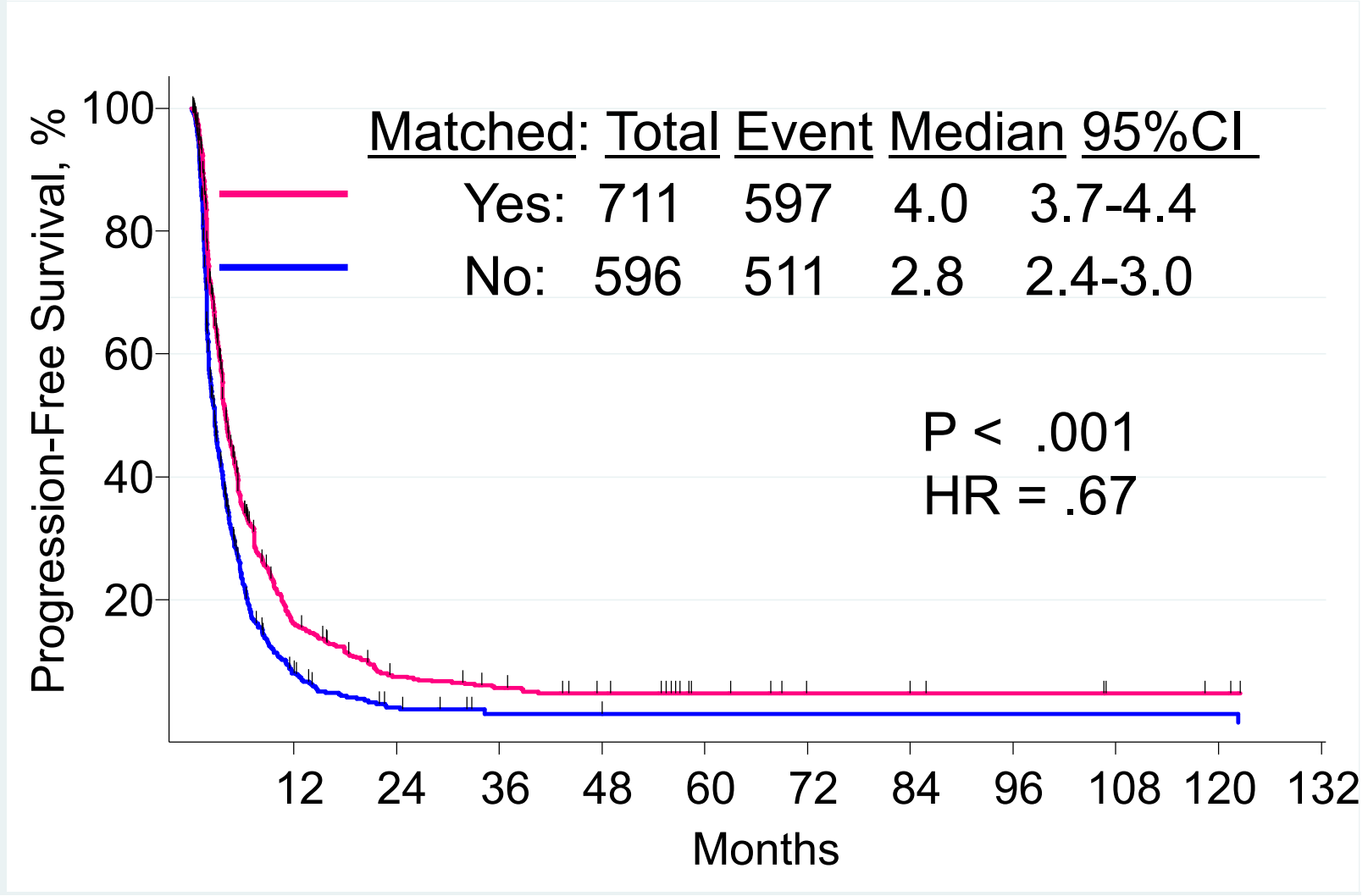
www.clinicaltrials.gov NCT00851032

IMPACT: Results

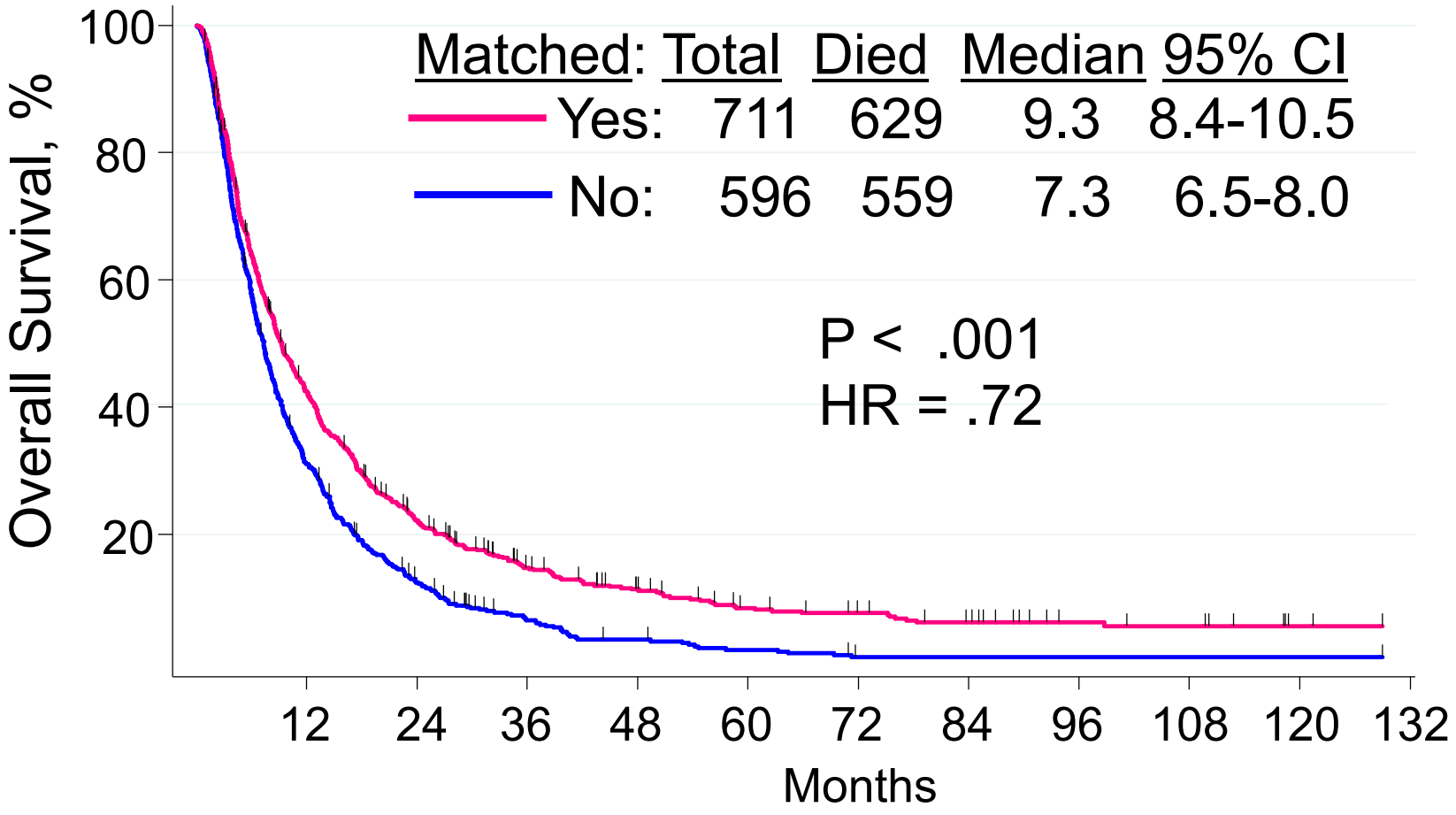
- Molecular testing: N = 3,743 (2007-2013)
- 1,307 (34.9%): ≥1 targetable molecular alteration
- 711 (54.4%): matched targeted therapy; 596 (45.6%) non-matched therapy.
- Median age: 57 yrs (range, 16-86); 39%, men.
- Median no. of prior therapies, 4 (range, 0-16); previously untreated = 2.8%
- Cancers: gastrointestinal, 24.2%; gynecological, 19.4%; breast, 13.5%; melanoma, 11.9%; lung, 8.7%.

Response, evaluable	Matched, N = 697	Non-matched, N= 571	*P*
Objective response, %	16.2	5.4	
Stable disease ≥ 6 months, %	18.7	14.7	
Total, %	34.9	20.1	<.001

Progression-Free Survival by Type of Therapy

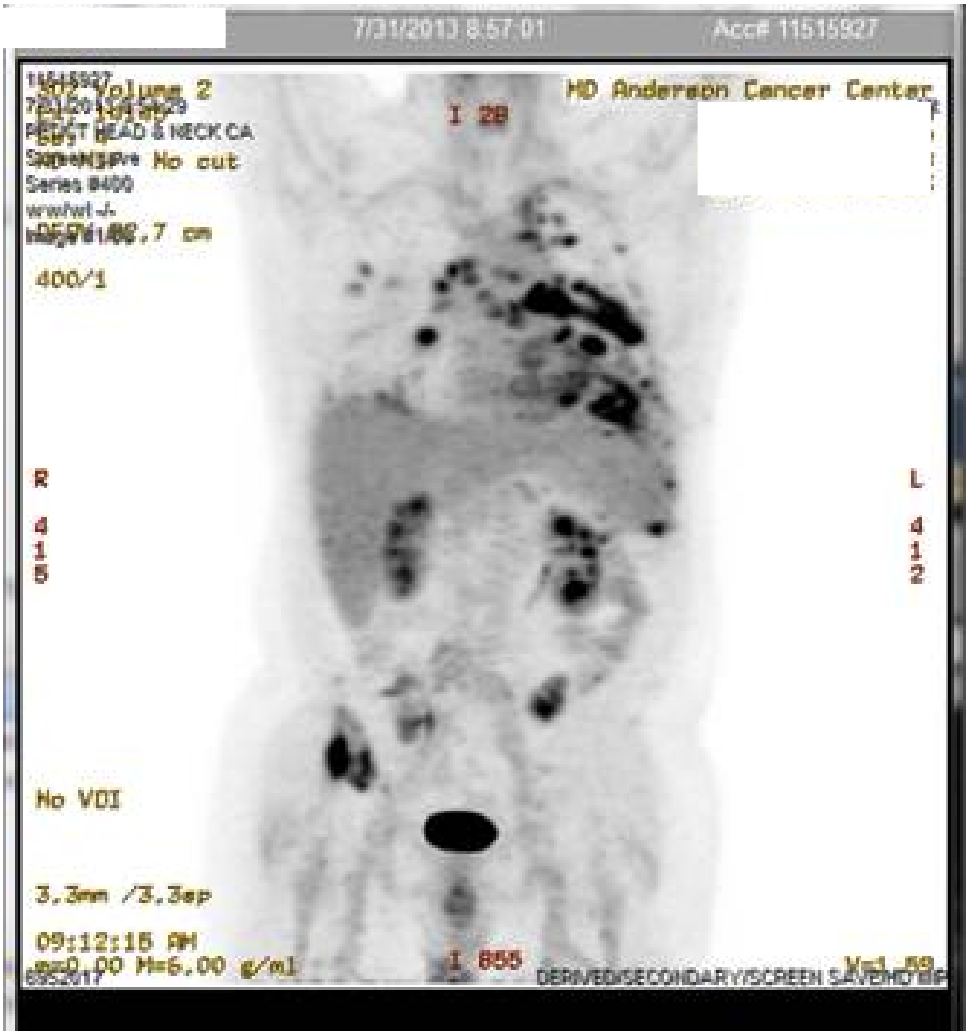


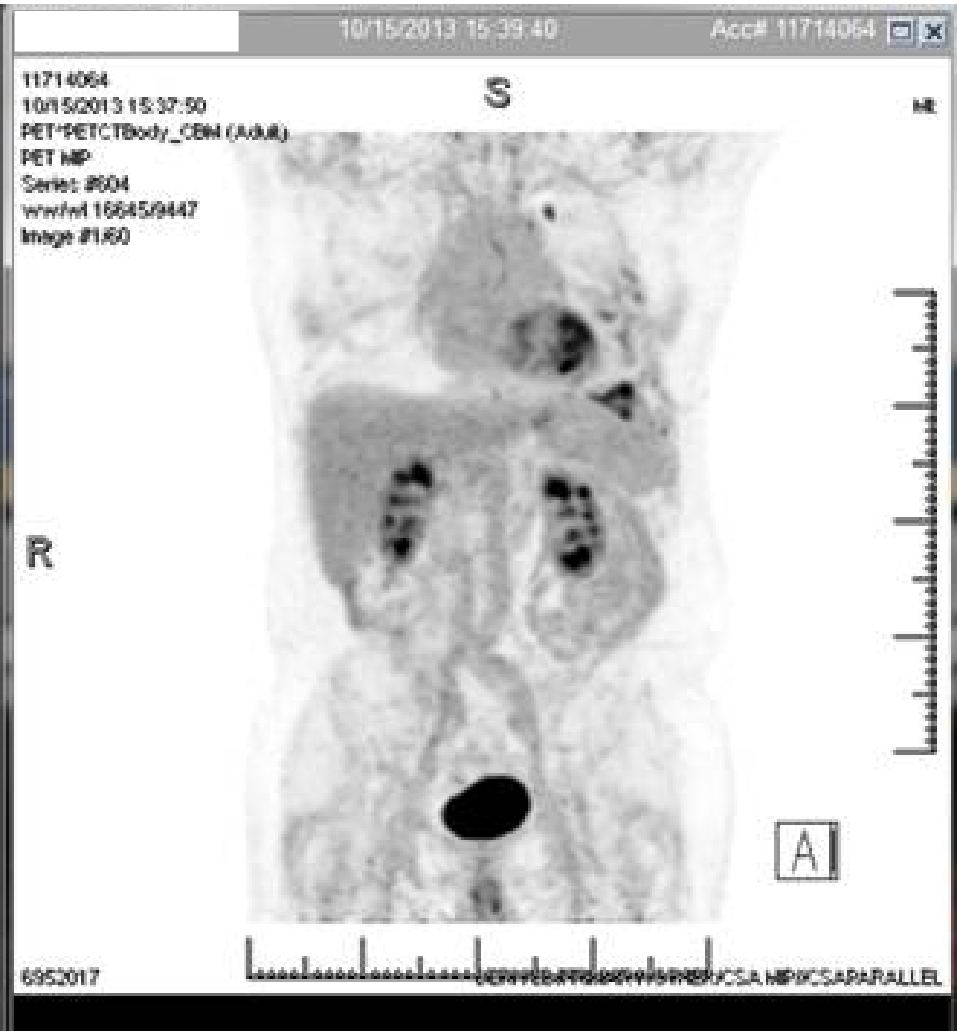
Overall Survival by Type of Therapy



3-yr OS, 15% matched vs. 7% non-matched; 10-yr OS, 6% vs. 1%, respectively

Precision Medicine in a Patient with Salivary Cancer (BRAF V600E Mutation, Vemurafenib)





THE ECONOMIST June 9, 2011

Taking aim sooner

If personalized medicine is to achieve its full potential, it should be used earlier on in clinical trials

Many scientists … believe that matching volunteers' genetic profiles to the drugs being tested will not only be better for the volunteers, but may also speed up the trials, and save millions of dollars in the process.

One such is Apostolia-Maria Tsimberidou of the University of Texas's MD Anderson Cancer Center, in Houston. And her preliminary results, presented at a meeting of the American Society of Clinical Oncology in Chicago, suggest she is right.

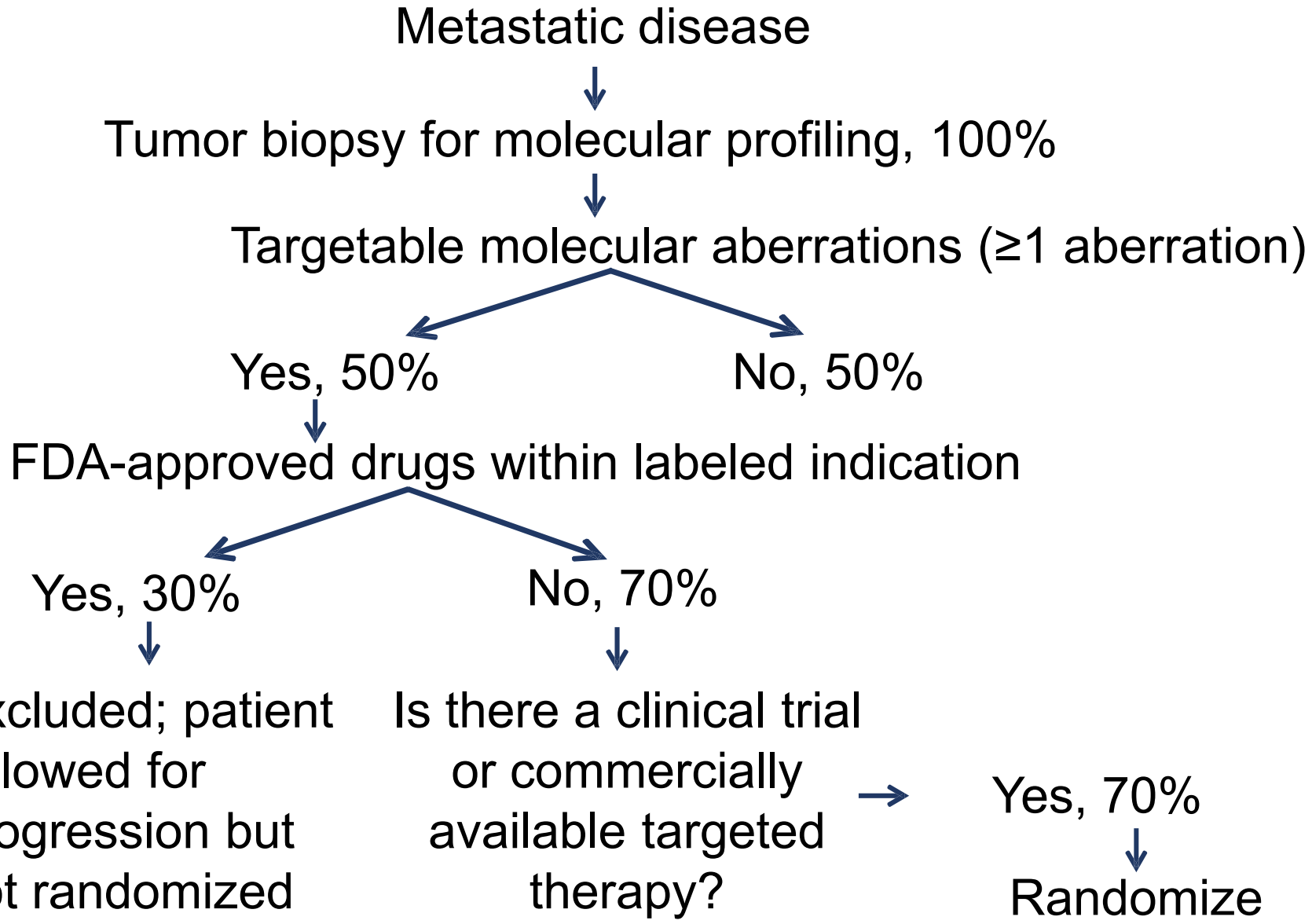
Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer (IMPACT 2)

Primary Objective

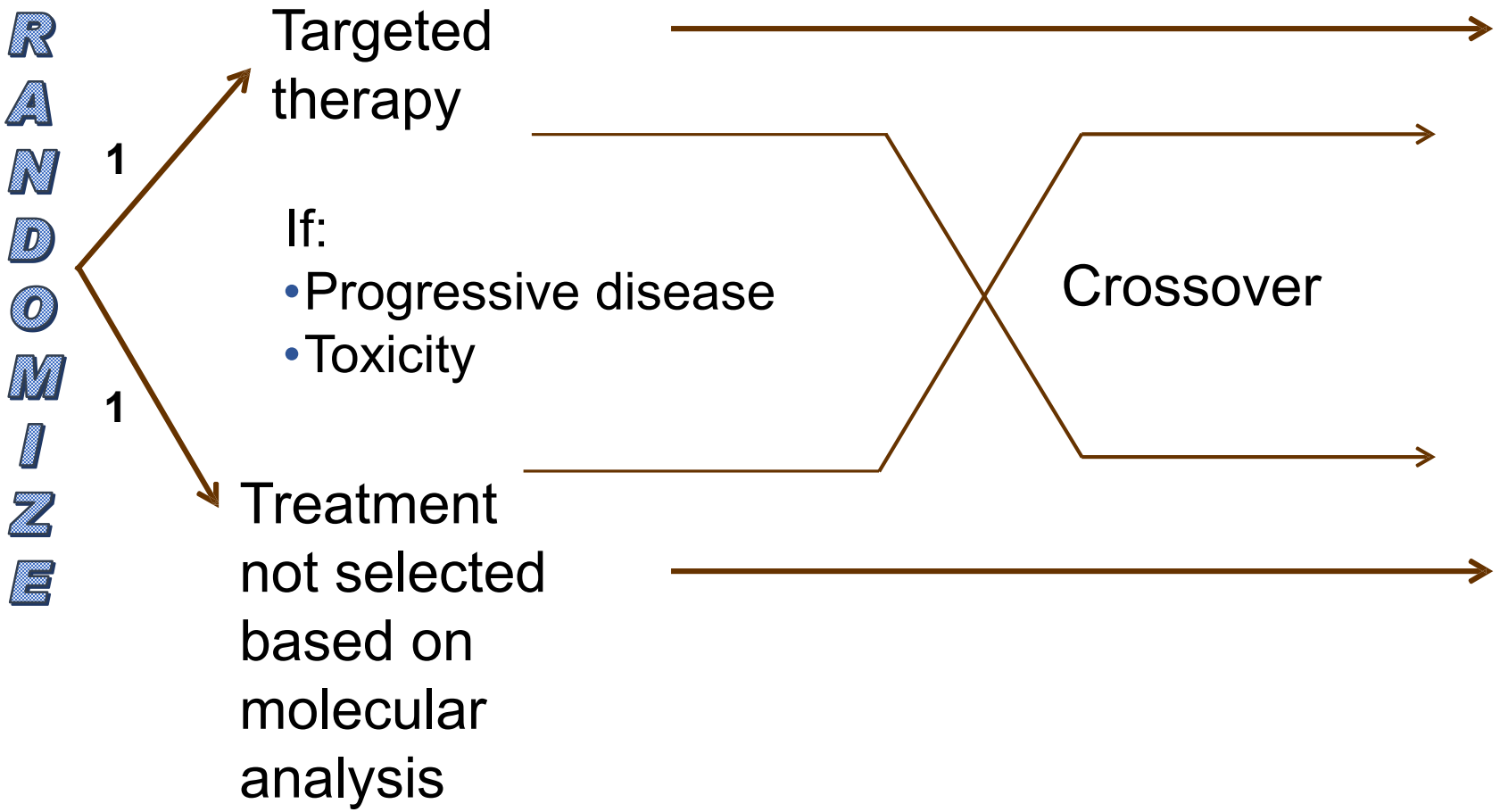
To determine whether patients treated with a targeted therapy selected on the basis of mutational analysis of the tumor have longer progression-free survival from the time of randomization than those whose treatment is not selected based on alteration analysis

PI: Tsimberidou, AM
www.clinicaltrials.gov NCT02152254
Supported in part by a research grant, initially from Foundation Medicine and currently from Tempus

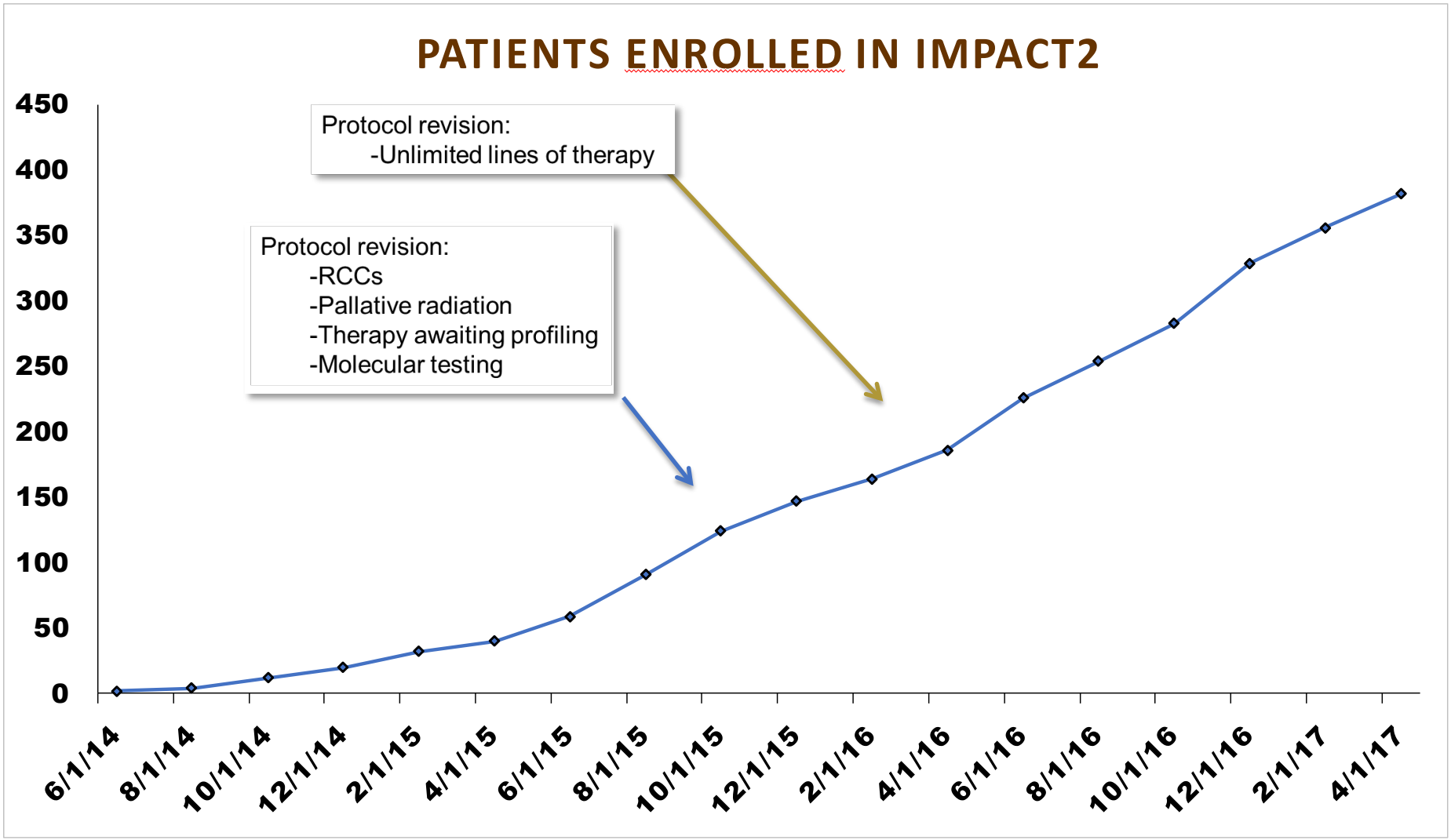
IMPACT 2. Study Design (I)



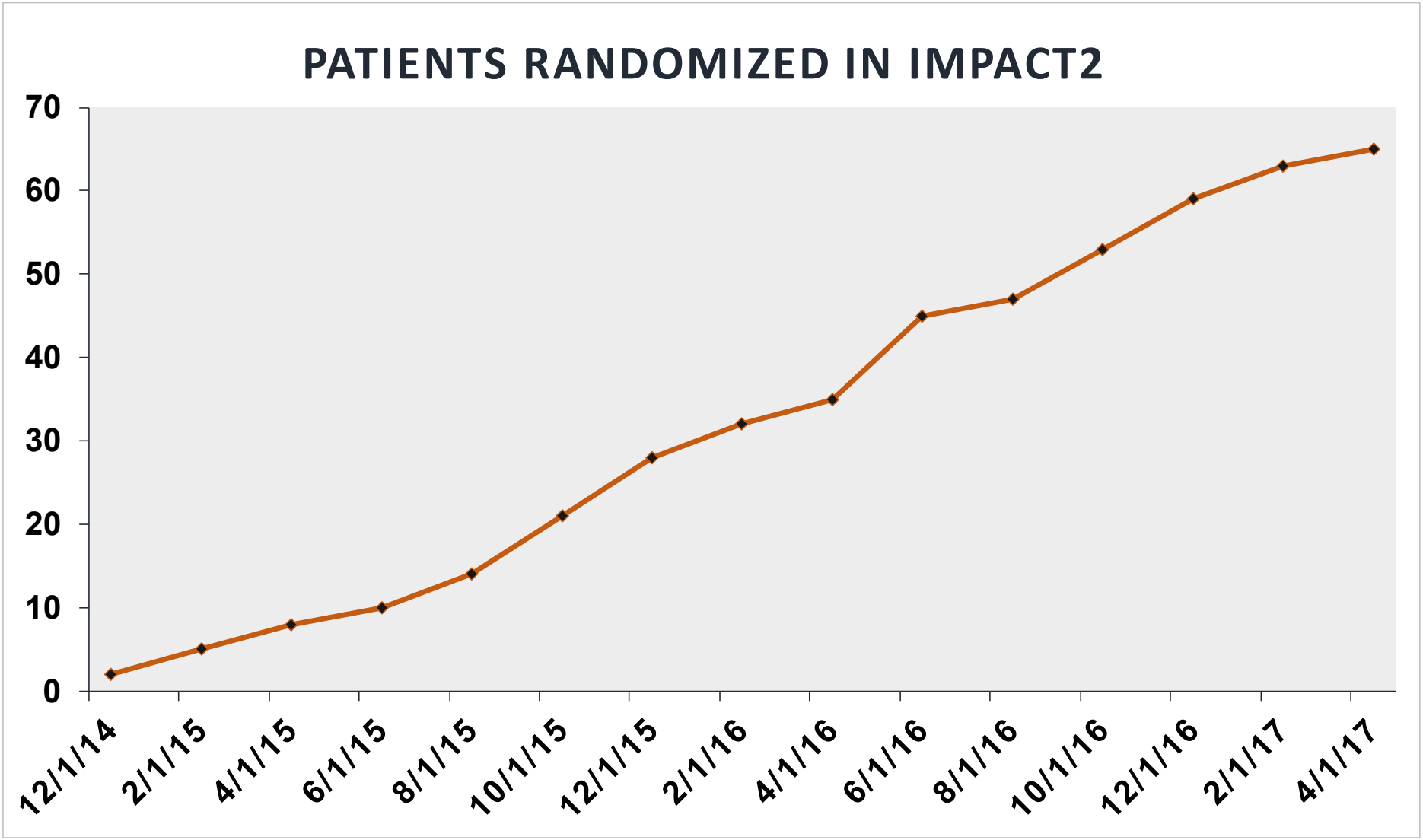
IMPACT 2. Study Design (II)



Cumulative plot of patients enrolled in IMPACT2



Cumulative plot of patients randomized in IMPACT2

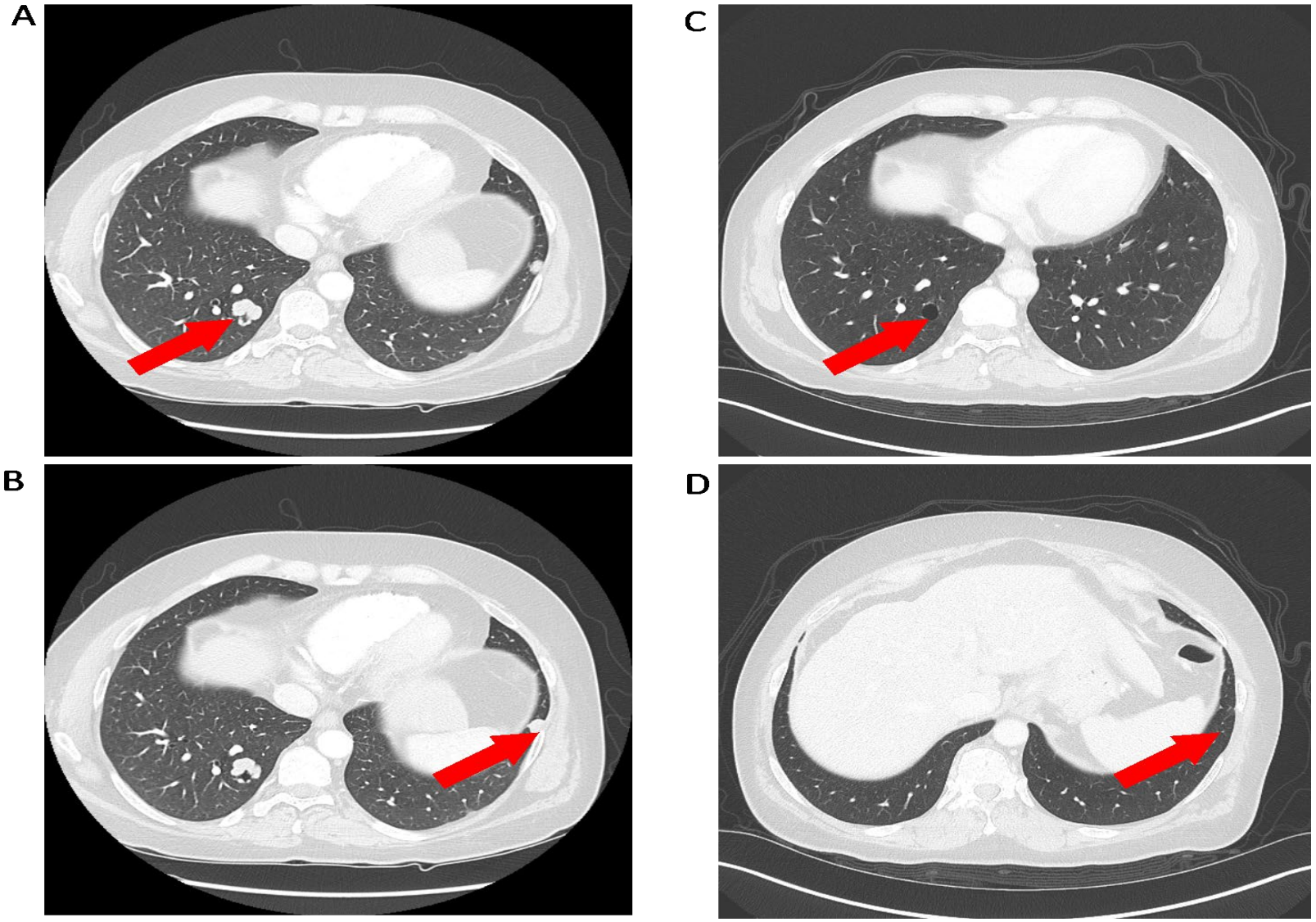


Head and Neck Squamous Cell Carcinoma with *FGF* Amplifications: CR to FGFR Inhibitor

Genomic Alterations	
FGF19 amplification	CHD2 D213N
FGF4 amplification	CREBBP R1392*
FGF23 amplification	EMSY amplification
FGF3 amplification	KDM5A amplification
FGF6 amplification	KRAS amplification
CCND1 amplification	MYC duplication exons 2-3
CCND2 amplification	TP53 E204*
CDKN2A/B loss	

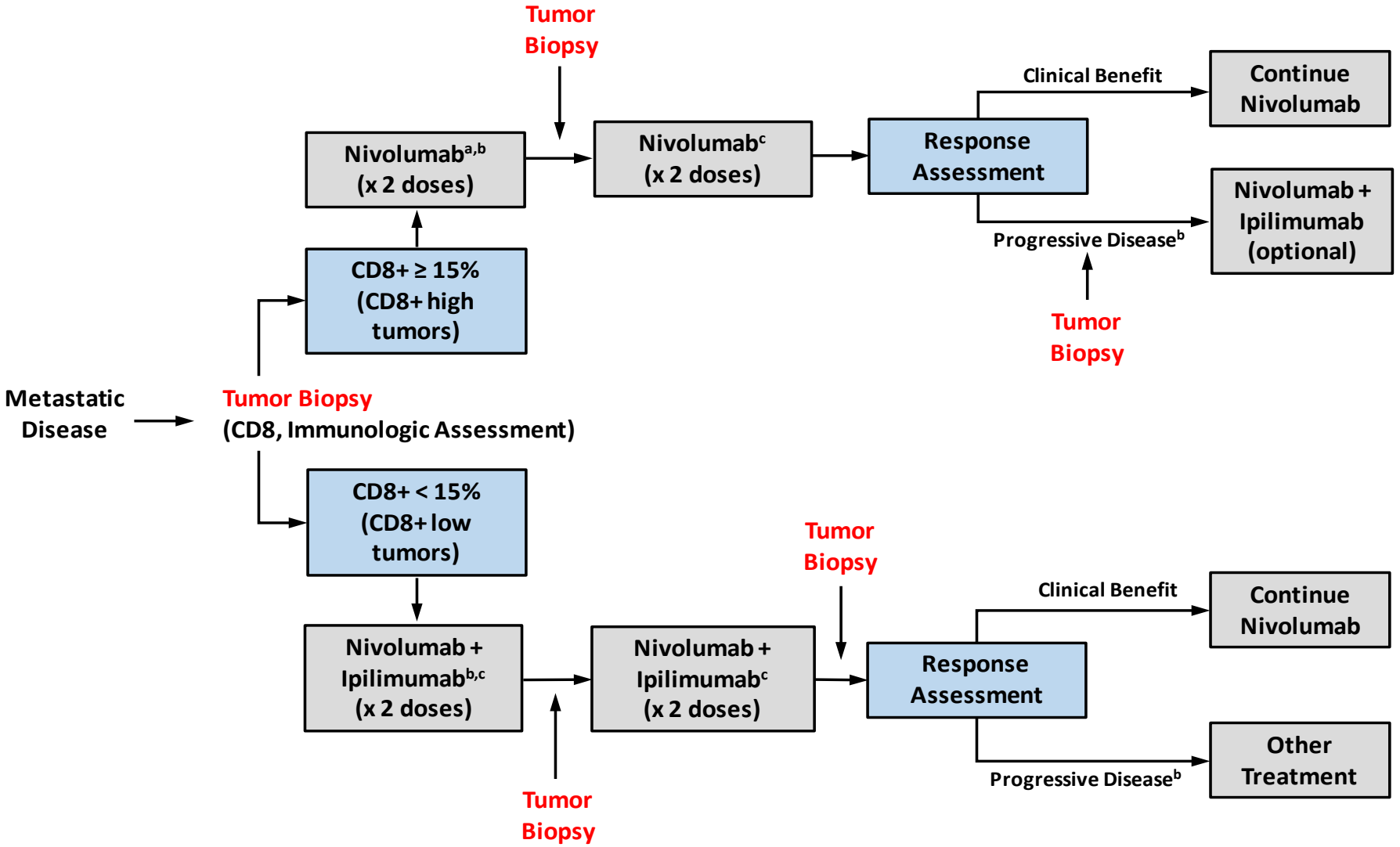
Dumbrava I, … Tsimberidou, AM, JCO Precision Oncology – In Press

Head and Neck Squamous Cell Carcinoma with *FGF* Amplifications: CR to FGFR Inhibitor



Dumbrava I, … Tsimberidou, AM, JCO Precision Oncology – In Press

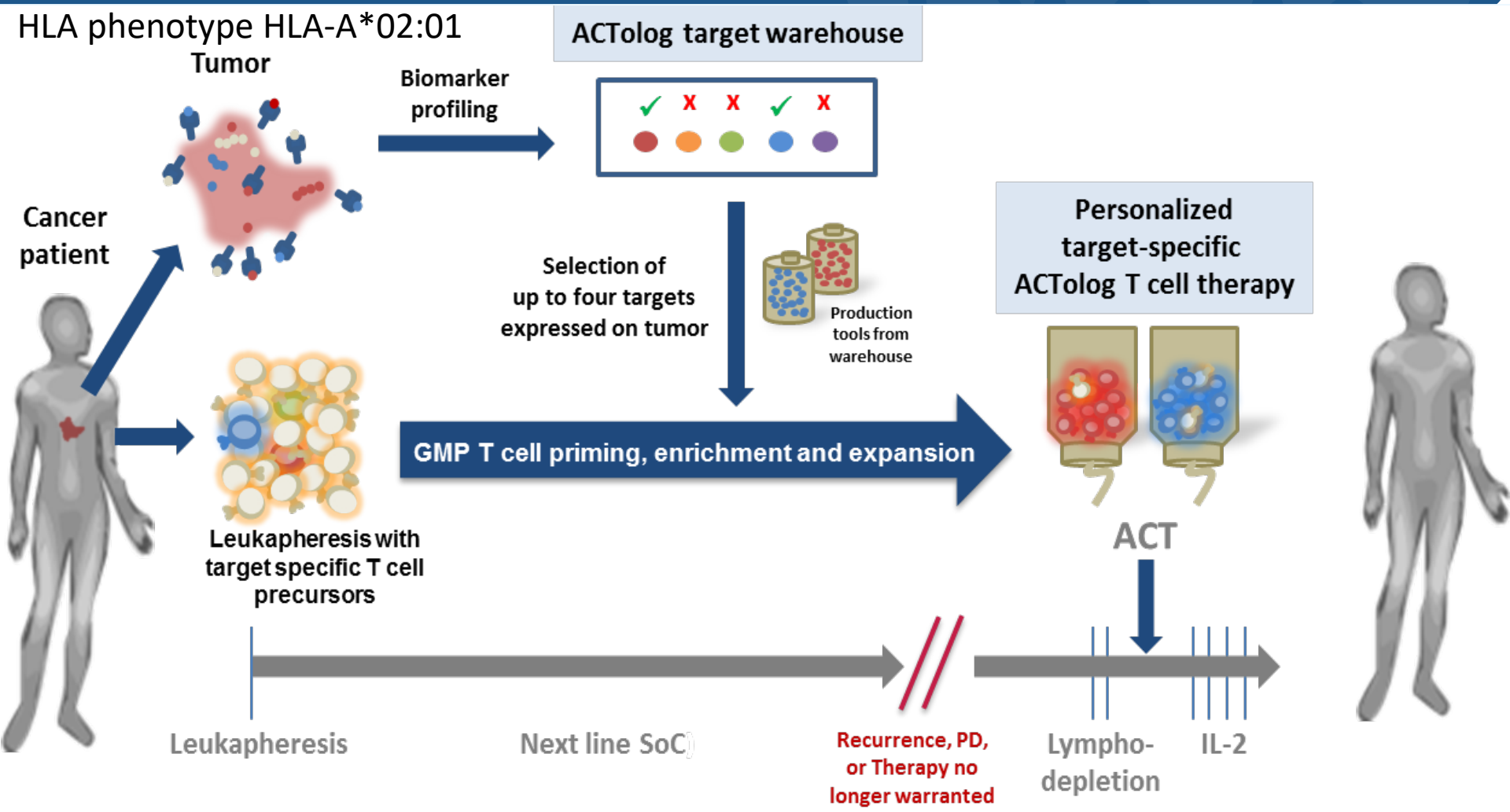
An Exploratory Study of Nivolumab with or without Ipilimumab According to Tumor CD8 Expression in Patients with Advanced Cancer



NCT03651271 Sponsored by Parker Institute for Cancer Immunotherapy

PI: AM. Tsimberidou, MD, PhD

ACTolog: Endogenous CD8+ T cells in Advanced Cancer



Screening	Production phase	Treatment/Observation	Follow-up

NCT02876510, Immatics *PI, AM Tsimberidou; Co-PI, Borje Andersson*

Challenges and Opportunities: Molecular profiling

	Actual	Goal
Tumor biopsy	Not standard	Standard of care
Tumor sequencing	Targeted NGS	Whole genome sequencing, immune markers, transcriptomics, proteomics
Bioinformatics	Limited	Optimized
Emergence of sub-clones	Limited data	Real-time monitoring
Time to analysis	>10 days	1-3 days
Timing	Advanced, refractory	Starting at diagnosis
Biomarker development	Drug-specific	Platform diagnostics
Tumor heterogeneity	Single lesion biopsy/ctDNA	Validated ctDNA analysis

Challenges and Opportunities: Clinical Trials/Drugs

	Actual	Goal
Drug discovery	Limited	More, effective drugs
Study design	Phase I, II, III	Adaptive, “N of 1”, umbrella protocols
Patient eligibility	≈5-30% of patients	100% of patients
Histology-agnostic trial	Small sample; unbalanced data; response heterogeneity	Novel design for interim analyses; Adaptive design*
“Targeted” drug definition	Imprecise	Precise
Targeted therapy selection	Subjective	Evidence-based, tumor board, artificial intelligence
Adaptive learning, “N of 1”	<10%	100%

* Early assessment of safety/clinical benefit of a drug permits inclusion of multiple stages of drug development in a single trial

Faster, Better, Smarter Trials Require (I):

- More patients to have “state of the art” comprehensive profiling (genomics, transcriptomics, immune markers, proteomics, novel markers)
- Profiling starting at diagnosis. Most studies offer drugs to patients who have received multiple lines of therapy; not a setting for optimal results
- More targeted, effective drugs/therapeutic strategies
- Information regarding available trials to doctors or patients to increase patient referral

Faster, Better, Smarter Trials Require (II):

- Better methology: (current model: single drug for single aberration). Comprehensive profiling, clinical outcomes, advanced analyses:

  (1) to offer matched therapy to more patients;

  (2) to compare outcomes to those of patients not receiving matched therapy (case-control comparator) and

  (3) to address complex questions that integrate precision molecular findings with immunologic findings to offer better treatments

Implementation of Precision Medicine

- Precision Medicine uses targeted therapy, immunotherapy, and other strategies to target specific biological abnormalities causing carcinogenesis in individual patients.
- Precision Cancer Medicine requires:

1. Complete understanding of tumor biology, including immune features, that drives carcinogenesis
2. Use of effective drugs and therapeutic strategies that inhibit carcinogenesis (rigorous definition)
3. Access to testing and effective drugs for all patients starting at diagnosis and during the course of their disease

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Thank you!

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